Original paper

SUMMARY
Bone metastases of breast cancer since recently, among others, are treated with Zolendric acid. Often in the world are mentioned necroses of mandible surrounding mucosa and oral cavity in such patients, with unproven causal relation. First time at the Department of Maxillofacial Surgery of the Clinical Center Sarajevo verified the two cases with the same pathology. Goal of this review is to show the social aspect of medical treatment of the mouth, which has great significance. Dilemmas are present, on how to treat, as surgically well as with medications. Results of treatment are not satisfactory since it stems to mutilate the patient, in terms of functional and aesthetic deficit, and that the duration is unfavorable for the community and patients. Open dilemma remains how to create algorithms (protocols of treatment and post surgical resocialization).

Key words: Bone metastases, Zolendric acid, Breasts cancer, Mandible necrosis, Resocialization.

1. INTRODUCTION
Bisphosphonates (BP) are analogues to endogenic pyrophosphonates, potential inhibitors of osteoclasts for indirect bone resorption. Bisphosphonates accumulates in the bone and act on the function of osteoblasts when they are released during bone remodeling. There are several ways of action: inhibition of precursor osteoclasts cells, synchronizing migratory and adhesive characteristics and induction of osteoclasts apoptosis. In addition, described are the effect on angiogenesis, micro-environment and signal converting between osteoclasts and osteoblasts (1, 2).

Bisphosphonates are approved for treatment of osteoporosis, Paget’s disease, hypercalcemia related to malignant tumors and bone affected with multiple myeloma or solid tumors. In clinical use are the following bisphosphonates products: Clodronate, Pamidronate, Alendronate, Ibandronate, Zolendronate, Risedronate. Known side effects of bisphosphonates therapy include transient “acute reaction”, nephrotoxicity, gastrointestinal side effects and hypocalcaemia (3, 4). In 2003 Marx RE et al published first comprehensive article on jaw osteonecrosis (ONJ) associated with action of bisphosphonates based on 36 cases (4). After that e more authors reported this complication in studies on larger and smaller sample, as well as individual cases (5, 6). Although ONJ is considered to be rare side effect, recent research by Durie et al who conducted a web-based survey on 1203 patients with Multiple Myeloma Manifesto (904) and breast cancer (299) who received intravenous bisphosphonates, find the confirmed or suspect ONJ in 12.8% of patients with MM and in 12% of patients with breast cancer. Among these patients after 36 months of bisphosphonates use ONJ occurs in 10% of cases that have received zolendronate and 4% pamidronate (7). Following data from 1998 to 2004 Research on Adverse Drug Events and Reports (RADAR) have identified 561 cases of ONJ among patients with cancer who receive Zolendronate (8), and since 2005 until now 126 cases were reported in literature (9, 10).

In the absence of uniform definitions the American Academy of Oral and Maxillofacial Surgeons (AAOMS), American Society for Bone and Mineral Research (ASBMR), as well as other groups established similar diagnostic criteria for bone necrosis of the jaws that occurs as a consequence of bisphosphonates therapy (11). According to the consensus of ASBMR bone necrosis of both jaws is defined as “exposure of the maxilla bone, mandible or both jaw that persist for at least 8 weeks, with the absence of prior irradiation and metastatic processes of the bones.” It is expected that with the new data working definitions will be improves (11).

Etiology and pathogenesis still remains insufficiently characterized, with uncertainty regarding the starting point (bone or soft tissue) and the role of bisphosphonates. Although many of the researches until now were focused on the bone as a starting point, in recent times it has been suggested that with bisphosphonates induced toxicity on oral mucosa may lead to poor healing of the traumatic lesions that occurs in soft tissue with a further extension to the bone lesions (12). Toxicity of the bisphosphonates on the epithelial cells is clearly documented (13).

Risk factors include trauma, female gender, older age, regions of the jaw without teeth, radiotherapy, chemotherapy, steroid therapy, blood problems / metastasis disease, anemia, coagulopahies, oral surgery procedures, alcohol drinking or smoking, early infections, and therapy with bisphosphonates (14).

Clinical signs and symptoms may be unnoticed for many weeks or months, and this phenomenon can be recognized only by noticing exposed bone in the oral cavity. These lesions often become symptomatic.
when the secondary infection occurs or trauma of the soft tissue through exposure to the sharp bone edges. Typical signs and symptoms include pain, exposure of the bone, and island of soft tissue, infection, tooth loss and drainage of the content (15).

2. PATIENTS AND METHODOLOGY

We observed 2 patients with clinical signs of oral mucous membrane defect over the upper parts of the horizontal mandible branches which featured open non necrotic bone of the alveolar mandible processus, clinical and x-ray diagnostics (CT, orthopantomogram and native projections)

In the first moments, based only on clinical picture there was a suspicion on oral cancer, as a secondary deposit, since the patients underwent chemotherapy (situation after breast cancer treatment on right or left side). Both patients had verified bone metastases in the thoracic part of the spine, which is among other things, lead to clinical suspicion of a secondary (malignant) deposit in the lower jaw. Respondents were females, completely toothless, and suffered from diabetes, chronically smokers, and in both cases there was permanent micro traumas of the oral mucosa of mechanical cause (during chewing of food) with a common secondary infection, so that at the end the local situation culminated in a large opening in the projection of horizontal mandible branches mandible with prominent bone parts of the alveolar reef, which was completely necrotic. Usually this local status changes was within half to one year after treatment with Zolendric acid as inhibitor osteoclasts bone resorption which among other things was used for treatment of bone metastasis of breast cancer.

In the early stages of clinical treatment of patients we made test biopsy with hormonal treatment with high doses of antibiotics and the continuous implementation of the treatment of pain. Test biopsy was repeated in both patients on three separate occasions, given the disproportion of the pathohistology results and clinical picture. We were convinced that this is a malignant disease that is in couple occasions in the preliminary results of pathohistology analysis suggested. After the third negative definitive results of pathohistology analysis completely rejected was the clinical suspicion of malignant disease, and we turn to treatment of necrotic infected tissues in the oral cavity (mucosa and bone structures), both with hormonal and surgical treatment. On several occasions (almost every three weeks) patients were treated surgically in terms of excohleation of the necrotic soft mass and bone structure with the provision of high doses of antibiotics and pain medication. We were in constant questions to continue this treatment or do something quite different, quite radi-
cally (resects full horizontal mandible arm and exudate large surface of the oral mucous membrane with or without primary reconstruction of post surgical defects. After suffering for more than several months, both patients had radical treatment, with partial resection of the mandible, removal of the necrotic peripheral mucosa, and removal of the mucous membranes without the primary reconstruction, since the peripheral atrophy of the soft structure was quite weak as a consequence of the conducted radiation and chemotherapy.

Post surgical defect was in the large degree of disfigurement in the functional and aesthetic sense. Weak function of chewing food, slurred speech and difficulty swallowing are difficult to patient’s everyday life (family and work obligations). Both of the patients are facing difficult surgery of secondary reconstruction of complex free tissue compositions (Fibula free flap and similar).

3. RESULTS

Partial necrosis of the surrounding oral mucosa of mandible is confirmed both clinically and with pathohistological analysis in patients who were treated with Zolendric acid. At this moment is not possible to prove the causal relation (pathogenesis), but there are many studies that point to the same above-mentioned situation, and offer the guide to prevent the formation and treatment of already formed local changes (16).

This article the first time in Bosnia and Herzegovina makes reference to the local pathological condition in oral cavity in patients treated with Zolendric acid. Manner and results of the treatment of our hospital practically match with proposed treatment by the American Academy of Oral and Maxillofacial Surgeons (AAOMS).

4. DISCUSSION

Local state of mandible bone necrosis and the surrounding mucosa are rare in the World for the patients who were treated with Zolendric acid due to bone metastasis of breast cancer. Normal protocol for treatment of breast cancer is usually carried out with every patient, and treatment protocol for pathological condition in oral cavity in such patients in the world is still not uniform. There are suggestions of AOOMS and ASBMR for prevention and treatment of patients with established bone necrosis of the jaw that is not different from the way of treatment applied to our patient, as well as final results, which are for us at this moment unsatisfactory given the large deficit in the function which involved the lower jaw, and not to mention the high aesthetic disfigurement. The general treatment protocol for the defects of free tissue compositions can not be incorporated in the general condition of these patients given that patients are usually in full dose irradiated and treated with chemotherapeutics, and they are usually chronically ill patients at older age. From the social and medical aspects, because of dilemmas in selection of treatment due to which patients are usually unnecessary treated for longer time, and for which the community devotes enormous resources (treatment of high doses, usually with last generation of antibiotics, which are enormously expensive, continuous treatment of pain, all in the framework of hospital treatment and at the end of more than one surgery in the intervals of one to two months. How to rehabilitate these patients and include them in the normal flow of life is a new dilemma to which at this moment there are no answers, so the patients are on the responsibility of the community.

5. CONCLUSION

Pathohistological finding confirmed partial mandible necrosis with part of the necrotic surrounding oral mucosa in two patients with breast cancer, treated surgically, with irradiation and with Zolendric acid for bone metastasis. Causal relation between these changes and local effect of the Zolendric acid (pathogenesis) is not proven. There are major dilemmas in the treatment of local status in oral cavity (weather to start with conservative surgical treatment or immediately choose the radical surgery). Duration of treatment and the final result shows the great social

<p>| Table 1. Clinical overview of general and local state |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|</p>
<table>
<thead>
<tr>
<th>PATIENT</th>
<th>Breasts Ca</th>
<th>Bone metastases</th>
<th>Irradiation</th>
<th>Chemotherapy (Zolendric acid)</th>
<th>Mandible necrosis</th>
<th>Oral mucosa necrosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PH confirmed and surgically treated</td>
<td>PH confirmed</td>
<td>Received full irradiation dose</td>
<td>Applied on ten occasions with 28 days pause</td>
<td>PH confirmed</td>
<td>PH confirmed</td>
</tr>
<tr>
<td>2</td>
<td>PH confirmed and surgically treated</td>
<td>PH confirmed</td>
<td>Received full irradiation dose</td>
<td>Applied on ten occasions with 28 days pause</td>
<td>PH confirmed</td>
<td>PH confirmed</td>
</tr>
</tbody>
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<p>| Table 2. Manner and duration of treatment |
|-----------------|-----------------|-----------------|-----------------|</p>
<table>
<thead>
<tr>
<th>PATIENT</th>
<th>Medication treatment</th>
<th>Surgical treatment</th>
<th>Duration of treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ceftriaxon, Tramadol chloride, Metamizole, Diazepam</td>
<td>Conservative surgical treatment on several occasions. Final radical surgical treatment.</td>
<td>6 on out-patient and hospital basis</td>
</tr>
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</table>
problem of such medical care. The selection of treatment, duration and final results of treatment at this moment does not give significant results that could in a short time return the patient in normal social and economic trends. Without mentioning financial costs to the communities that are present in the course of treatment for such patients.

REFERENCES

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